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The Dow Chemical Company
Midland, MI 48674
USA

1803 BUILDING

8EHQ-12-18775

August 07, 2012

CONFIDENTIAL BUSINESS INFORMATION 40 CFR 2.201-2.215

VIA FEDERAL EXPRESS

Document Processing Center (7407M)
(Attn: TSCA Section 8(e) Coordinator)
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
1201 Constitution Avenue, NW
Washington, DC 20004-3302

88120000318/S

Generic Name: Halogenated Pyridine derivative

Dear Sir/Madam:

The following information is being submitted by The Dow Chemical Company (Dow) pursuant to current guidance issued by EPA indicating EPA's interpretation of Section 8(e) of the Toxic Substances Control Act. Dow has made no determination as to whether a significant risk of injury to health or the environment is actually presented by the findings.

During a one year dietary toxicity study male and female Beagle dogs were fed diets containing 0 (control), 500, 2500, or 10000 ppm in males, 0 (control), 500, 2500, or 10000/5000 ppm in females. The high-dose in female dose was reduced from 10000 to 5000 ppm on test day 47 because of body weight loss (average of 9%) at 10000 ppm during the first 6 weeks of treatment

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The kidney was the target organ for dogs during the 1-year study. Treatment-related kidney effects consisted of: 1) very slight degeneration with regeneration of renal proximal and distal tubules in 1/4 females given 2500 ppm, 2/4 males given 10000 ppm and 1/4 females given 10000/5000 ppm, 2) very slight degeneration of collecting ducts in 2/4 males given 10000 ppm and 1/4 females given 2500 ppm, 3) very slight multifocal fibrosis of the renal cortex in 1/4 males given 10000 ppm, 4) very slight multifocal glomerulosclerosis in 2/4 males given 10000 ppm and 1/4 females given 10000/5000 ppm, and 5) the presence of focal or multifocal granulomas in the cortex of 1/4 males given 10000 ppm and 1/4 females given 10000/5000 ppm. The kidney effects involved less than 1% of the renal parenchyma in all of the affected animals.

Questions may be addressed to the undersigned,

Sincerely,

Alicia M Fitzpatrick

Alicia M. Fitzpatrick
PH: 215-785-7033
FAX: 215-785-7227
E-MAIL: afitzpatrick@dow.com
bls

Attachment

Attachment 1

Substantiation Questions

1. ***Is your company asserting this confidential business information (CBI) claim on its own behalf? If the answer is no, please provide company name, address and telephone number of the entity asserting claim.***

   We are submitting this claim on behalf of ourselves.

2. ***For what period do you assert your claim(s) of confidentiality? If the claim is to extend until a certain event or point in time, please indicate that event or time period. Explain why such information should remain confidential until such point.***

   This is an early-stage research chemical which is not currently available for commercial use and as a consequence, it is difficult to estimate if, or when, it might be commercially available. As a consequence, our claim(s) for confidentiality should be maintained indefinitely or until the chemical has been disclosed on the Toxic Substances Control Act (TSCA) Chemical Inventory.

3. ***Has the chemical substance information that you are claiming as confidential been disclosed to any other government agency or to this Agency at any other time? Identify the Agency to which the information was disclosed and provide the date and circumstances of the same. Was the disclosure accompanied by a claim of confidentiality? If yes, attach a copy of said document reflecting the confidentiality agreement.***

4. ***Briefly describe any physical or procedural restrictions within your company relating to the use and storage of the information you are claiming CBI.***

   Information on the chemical identity and other data for this substance are marked "CONFIDENTIAL" or "RESTRICTED" and may not be disclosed outside the company without a Confidential Disclosure Agreement. Documents so classified are clearly stamped and may not be reproduced without permission.

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BUSINESS INFORMATION
40-CFR 2.201-2.215

5. ***If anyone outside your company has access to any information claimed CBI, are they restricted by confidentiality agreement(s)? If so, explain the content of the agreement(s).***

The chemical identity of this substance has not been disclosed outside of The Dow Chemical Company except in the Patent applications referenced in question 3 or to a limited number of companies bound by confidentiality agreements that cover our information being claimed CBI.

6. ***Does the information claimed as confidential appear or is it referred in any of the following:***
   a) ***advertising or promotional material for the chemical substance or the resulting product;.***
   b) ***material safety data sheets or other similar materials (such as technical data sheets) for the substance or resulting product(include copies of this information as it appears when accompanying the substance and/or product at the time of transfer or sale);***
   c) ***Professional or trade publications; or***
   d) ***Any other media or publications available to the public or to your competitors.***

If the answer is yes to any of the above, indicate where the information appears, include copies, and explain why it should nonetheless be treated as confidential.

The chemical identity and CAS# of the subject material has not been disclosed in any of the documents listed above.

7. ***Has EPA, another federal agency, or court made any confidentiality determination regarding information associated with this substance? If so, please provide copies of such determinations.***

No, to the best of our knowledge, the EPA, another federal agency, or court has not made any confidentiality determination regarding this substance.

8. ***Describe the substantial harmful effects that would result to your competitive position if the CBI information is made available to the public. In your answer, explain the casual relationship between disclosure and any resulting substantial harmful effects. Consider in your answer such constraints as capital and marketing cost, specialized technical expertise, or unusual processes and your competitors' access to your customers. Address each piece of information claimed as CBI separately.***

We assert that disclosure of the chemical identity and CAS# would likely result in substantial harm to our competitive position. While patent applications have been published, our company files and maintains patent applications on many

chemicals that ultimately are not commercialized. It is our position that release of this chemical identify information would communicate an intent for commercial development of this specific chemical to our competitors. This intent is only known to certain persons within The Dow Chemical Company or within a limited number of other companies, all of which are bound by confidentiality agreements. Public disclosure of the chemical identity would enable competitors to avoid research and development costs, as well as potentially limit our future commercial opportunities.

9. Has this substance been patented in the U.S. or elsewhere? Is a patent for the substance currently pending?

This substance has been patented in the U.S. U.S. patent applications and PCT patent applications have published and additional patents are pending. Although the chemical identity of this substance is published in these patent applications, it is commonly included with the identities of other analogs.

10. Is this substance/product commercially available and if so, for how long has it been available on the commercial market?

a) If on the commercial market, are you competitors aware that the substance is commercially available in the U.S.?

b) If not already commercially available, describe what stage of research and development (R&D) the substance is in, and estimate how soon a market will be established.

c) What is the substance used for and what type of product does it appear in?

The chemical substance is not commercially available in the United States or elsewhere.

a). This is not relevant as the chemical is not commercially available in the United States.

b). The chemical substance is at a very early stage in our new product research and development process. As a consequence, it is difficult to estimate if or when a market might be established.

c). The chemical substance is being used for research purposes.

11. Describe whether a competitor could employ reverse engineering to identically create the substance.

Disclosure of the chemical identify of the substance would obviate the need for a competitor to use reverse engineering and enable it to immediately create the identical substance and test its specific commercial utilities.

12. Do you assert that disclosure of this information you are claiming CBI would reveal:

a) confidential processes used in manufacturing the substance
b) if a mixture, the actual portions of the substance in the mixture; or
c) information unrelated to the effects of the substance on human health or the environment?

Answers:

a). No.
b). No.
c). Disclosure of the confidential chemical identity would not be related to the effects of the substance on the environment or human health since the generic terminology used should be sufficient at this stage for public interest.

13. Provide the Chemical Abstract Service Registry Number for the product, if known. Is your company applying for a CAS number now or in the future? If you have applied for a CAS number, include a copy of the contract with CAS.

The CAS number for this substance is

14. Is the substance or any information claimed CBI the subject of FIFRA regulation or reporting? If so, explain.

No.

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Fisher (F344/DuCrl) rats, 60/sex were fed diets formulated to provide 0, 20, 100, 400, 625 (males) or 750 (females) mg/kg/day of the test substance for up to 2 years.

The cumulative mortality of males given 625 mg/kg/day at 24 months was higher and statistically significant as compared to controls (62% vs 32%, respectively). The higher mortality was attributed to treatment-related toxic effects in the kidneys. The increased mortality was not due to tumors, which indicates that this dose level had exceeded a maximum tolerated dose (MTD). A MTD was achieved for females given 400 mg/kg/day,

based on treatment-related degeneration with regeneration of renal tubules and necrosis of renal tubular epithelial cells in some females at this dose level.

Males given 625 mg/kg/day had treatement-related statistically identified lower mean body weights at most measurement intervals starting on day 50 and continuing through day 729. On day 729, the mean body weight and body weight gain for males given 625 mg/kg/day were 7.9% and 10.2% lower than controls respectively. Males given 400 mg/kg/day had treatment-related statistically identified lower body weights first noted on day 176 and continuing through day 729. On day 729 the mean body weight and body weight gain for males given 400 mg/kg/day were 2.8% and 3.7% lower than controls. Females given 750 mg/kg/day had treatment-related statistically identified lower body weights, first noted on test day 344, and continuing through test day 512. On test day 512, the mean body weight and body weight gain for females given 750 mg/kg/day were 12% and 17.3% lower than controls, respectively. Females given 750 mg/kg/day were humanely euthanized on test day 518 due to excessive mortality exceeding 50%. The body weights and body weight gains of females given 20, 100 or 400 mg/kg/day and males given 20 or 100 mg/kg/day were unaffected by treatment with the test substance.

The only treatment-related effect on clinical chemistry parameters was a slightly higher statistically identified urea nitrogen concentration in females given 750 mg/kg/day at 12 months. The higher urea nitrogen corresponded with treatment-related histopathologic kidney effects at this time point.

Males given 400 or 625 mg/kg/day and females given 400 or 750 mg/kg/day had treatment-related statistically identified higher urine volumes and lower specific gravities at most of the sampling times of the study, relative to controls. These alterations corresponded with treatment-related histopathologic effects of renal tubules and/or collecting ducts in males given 400 or 625 mg/kg/day and females given 400 or 750 mg/kg/day. There was a general tendency for males given 400 or 625 mg/kg/day and females given 400 or 750 mg/kg/day to have slightly lower urine pH than controls during the first 12 months of the study. This non-adverse alteration was interpreted to be treatment related, likely due to the presence of the parent compound the test substance, a carboxylic acid and some of its acidic metabolites in the urine.

At the 12-month necropsy, males given 400 or 625 mg/kg/day had treatment-related statistically identified lower final body weights (7.4% and 5.5% lower than controls, respectively). Males given 400 or 625 mg/kg/day and females given 400 or 750 mg/kg/day

had treatment-related statistically identified higher absolute and/or relative kidney weights at 12 months. The higher kidney weights corresponded to hypertrophy of renal collecting duct epithelium at these dose levels. At the 24-month necropsy, males given 625 mg/kg/day had a treatment-related statistically identified 7.6% lower final body weight, relative to controls. Males given 400 or 625 mg/kg/day had treatment-related statistically identified higher relative kidney weights, and females given 400 mg/kg/day had statistically identified higher absolute and relative kidney weights. The higher kidney weights corresponded to degeneration with regeneration of renal tubules, hypertrophy of collecting duct epithelial cells, and hyperplasia of the pelvic epithelium at these dose levels.

During the second year of the study, the primary treatment-related gross pathologic observation was an increase in the incidence of roughened surface of the kidneys of males given 625 mg/kg/day and females given 750 mg/kg/day. The roughened surface of kidneys in males given 625 mg/kg/day corresponded to the histopathologic observation of degeneration with regeneration of renal tubules.

At 12 months, primary treatment-related histopathologic effects occurred in the kidneys of males given 400 or 625 mg/kg/day and females given 400 or 750 mg/kg/day. The effects consisted of an increased incidence of chronic progressive glomerulonephropathy (females only at 400 or 750 mg/kg/day), hyperplasia of the pelvic epithelium, hypertrophy of collecting duct epithelium, increased number of mitotic figures in the collecting duct epithelium, chronic interstitial inflammation of the medulla, necrosis of collecting duct epithelium (females only at 750 mg/kg/day), and vacuolization of collecting duct epithelium in the papilla. In the 24-month carcinogenicity phase of the study, numerous primary treatment-related histopathologic effects occurred in the kidneys of males given 400 or 625 mg/kg/day and females given 400 mg/kg/day. The effects at these dose levels consisted of: degeneration with regeneration of proximal and distal tubules, necrosis of individual tubular epithelial cells, hyperplasia of pelvic epithelial cells, hypertrophy of collecting duct epithelial cells, and chronic interstitial inflammation of the inner medulla. Additional treatment-related kidney effects consisted of the presence of calculi in the renal pelvis of one male given 400 mg/kg/day and two males given 625 mg/kg/day, increased incidence of slight mineralization of the pelvic epithelium in males given 625 mg/kg/day, necrosis of collecting duct epithelial cells in females given 400 mg/kg/day, and increased numbers of mitotic figures in collecting duct epithelial cells of females given 400 mg/kg/day. Primary treatment-related effects occurred in the urinary bladders of 3 males given 400 mg/kg/day

and 7 males given 625 mg/kg/day. The bladder effects consisted of slight to moderate, diffuse or focally extensive hyperplasia of the transitional epithelium, and very slight to slight subacute to chronic inflammation in the submucosa beneath the hyperplastic epithelium. One male given 400 mg/kg/day and two males given 625 mg/kg/day had microscopic calculi in the lumen of the urinary bladder that were interpreted to be treatment related. Treatment-related secondary histopathologic changes consisted of hypertrophy and vacuolization of the zona glomerulosa of the adrenal glands in males given 400 or 625 mg/kg/day, and an increase in the incidence of atrophy of mesenteric adipose tissue in males given 625 mg/kg/day. The hypertrophy of the zona glomerulosa of the adrenal glands was interpreted to be an adaptive response secondary to renal disease, and the adipose tissue atrophy was associated with body weight loss caused by renal disease in most cases.

Based on primary effects in the kidneys and urinary bladder of males at 400 mg/kg/day, and primary effects in the kidneys of females at 400 mg/kg/day, the No-Observed-Effect Level (NOEL) and the No-Observed-Adverse-Effect Level (NOAEL) for males and females was 100 mg/kg/day.

Questions may be addressed to the undersigned,

Sincerely,

Alicia M Fitzpatrick

Alicia M. Fitzpatrick
PH: 215-785-7033
FAX: 215-785-7227
E-MAIL: afitzpatrick@dow.com
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3. ***Has the chemical substance information that you are claiming as confidential been disclosed to any other government agency or to this Agency at any other time? Identify the Agency to which the information was disclosed and provide the date and circumstances of the same. Was the disclosure accompanied by a claim of confidentiality? If yes, attach a copy of said document reflecting the confidentiality agreement.***

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   The chemical identity and CAS# of the subject material has not been disclosed in any of the documents listed above.

7. ***Has EPA, another federal agency, or court made any confidentiality determination regarding information associated with this substance? If so, please provide copies of such determinations.***

   No, to the best of our knowledge, the EPA, another federal agency, or court has not made any confidentiality determination regarding this substance.

8. ***Describe the substantial harmful effects that would result to your competitive position if the CBI information is made available to the public. In your answer, explain the casual relationship between disclosure and any resulting substantial harmful effects. Consider in your answer such constraints as capital and marketing cost, specialized technical expertise, or unusual processes and your competitors' access to your customers. Address each piece of information claimed as CBI separately.***

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c) What is the substance used for and what type of product does it appear in?

The chemical substance is not commercially available in the United States or elsewhere.

a). This is not relevant as the chemical is not commercially available in the United States.

b). The chemical substance is at a very early stage in our new product research and development process. As a consequence, it is difficult to estimate if or when a market might be established.

c). The chemical substance is being used for research purposes.

11. Describe whether a competitor could employ reverse engineering to identically create the substance.

Disclosure of the chemical identify of the substance would obviate the need for a competitor to use reverse engineering and enable it to immediately create the identical substance and test its specific commercial utilities.

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- ***a) confidential processes used in manufacturing the substance***
- ***b) if a mixture, the actual portions of the substance in the mixture; or***
- ***c) information unrelated to the effects of the substance on human health or the environment?***

Answers:

a). No.
b). No.
c). Disclosure of the confidential chemical identity would not be related to the effects of the substance on the environment or human health since the generic terminology used should be sufficient at this stage for public interest.

13. Provide the Chemical Abstract Service Registry Number for the product, if known. Is your company applying for a CAS number now or in the future? If you have applied for a CAS number, include a copy of the contract with CAS.

The CAS number for this substance is [ ]

14. Is the substance or any information claimed CBI the subject of FIFRA regulation or reporting? If so, explain.

No.

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